Radiating Change

Ever since his training at Harvard Medical School, ***Kevin Camphausen, M.D.****, knew that his career would combine translational research with patient care. While at Harvard, he trained with C. Norman Coleman, M.D. (now Head of the Radiation Research Program, Extramural NCI), and worked with Judah Folkman, M.D., a pioneer of research into angiogenesis and tumor formation that has resulted in a new class of cancer therapies. As head of the Imaging and Molecular Therapeutics Section in the Radiation Oncology Branch at CCR, Camphausen has a rare opportunity to forge the bench-to-bedside connections that are so vital to the progress of radiation oncology. The branch handles approximately 450 consults per year for many different cancers in adults as well as children. Although his team will do consults and referrals for every patient that comes through the door, Camphausen and his colleagues are limited to treating those that fall within the inclusion criteria of one of their clinical trial protocols. Thus, they cannot treat everyone, but each patient they do treat is also part of research that will lead to a brighter future for others diagnosed with their disease.*

(*Photo:* R. Baer)

Kevin Camphausen, M.D.

Radiation oncology is based on the principle that tumor tissue is more sensitive to radiation damage than normal tissue. Ionizing radiation damages DNA. The same mutations that cause cancerous cells to rapidly proliferate by forfeiting normal cellular checkpoints and DNA repair mechanisms make these cells more vulnerable to the molecular damage inflicted by radiation. In addition, the rapid divisions of cancerous cells cause DNA damage to accumulate at an increasing pace as it is passed on to daughter cells until the progeny are ultimately no longer viable.

Radiation oncology branched off from Radiology as a clinical specialization more than 40 years ago in order to foster its own unique blend of expertise. To treat patients effectively, we have to understand and manipulate both biology and physics. On the physics side, we use one set of technologies to identify and delineate the tumor within the body—computed tomography (CT) and magnetic resonance imaging (MRI)—and another set of technologies to irradiate it—linear accelerators (Linac). We must decide on the more esoteric parameters controlling the beam of radiation as well as contend with the more mundane but equally challenging issues of making sure the physical placement of the patient (and hence his tumor) in the beam is accurate to within millimeters.

On the biology side, we need to determine which types of tumors are best treated focally and which require wider radiation beams; we need to balance treatment between the different sensitivities of normal tissue and tumors. And the greatest potential for advances in radiation oncology lies in a better understanding of tumor biology and in discovering new agents to sensitize cancer cells to radiation.

For me, combining laboratory research, clinical research, and clinical care is the most satisfying way to bring about advances in radiation oncology that will extend and improve patients' lives.

Glioblastoma Multiforme

Although the Radiation Oncology Branch (ROB) is involved in the treatment of a myriad of cancers, my own research focuses on brain cancers. Glioblastoma multiforme (GBM)—a cancerous proliferation of astrocytes, a type of "support cell" in the

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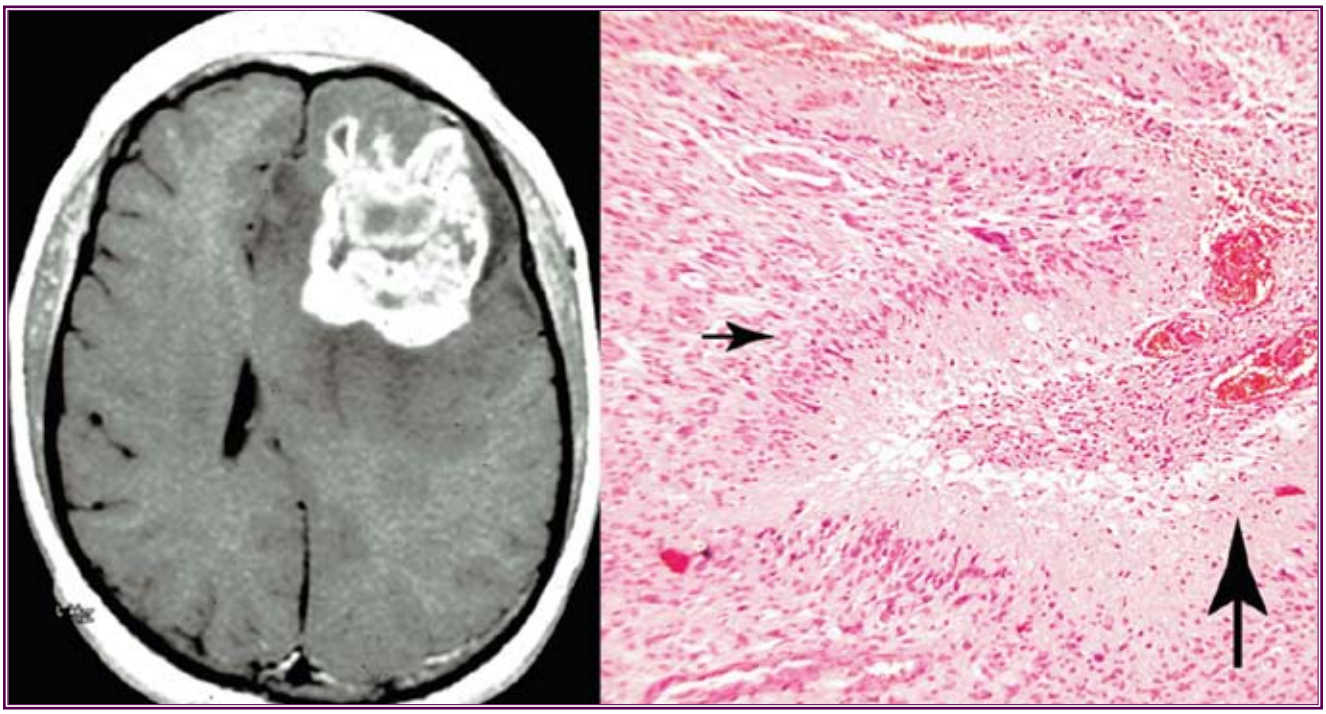

(*Image: Adapted from* Weil RJ, 2005; PLoS Med 3(1): e21. *doi*:10.1371/*journal.pmed*.0030031)

Images from a patient with glioblastoma multiforme (GBM). Magnetic resonance image of a large left frontal GBM taken one day before surgery *(left).* Tissue sample from the same tumor showing cellular proliferation and hemorrhage *(right, large arrow).*

brain—is the most common brain cancer with 20,000 new cases diagnosed yearly. This cancer is the same type of cancer that Senator Edward Kennedy was diagnosed with last year. We typically see patients in their 40s and 50s who, after having no previous history of neurological disorders, suddenly experience a seizure or another acute symptom that prompts a physician to order an MRI. It is not uncommon for the GBM to have invaded a large portion of the brain by then.

With the vast amount of information about cancer now available online, most cancer patients tend to be fairly knowledgeable about their disease—my colleague down the hall who specializes in prostate cancer will have patients come in with a three-ring binder full of information that they have downloaded from the Internet about their disease and treatment options. But GBM patients—who may otherwise be in the prime of life with small children under their care—are often shell-shocked. There is not a lot of time between diagnosis and treatment, and the prognosis, unfortunately, is not very good for these patients. The standard of care treatment is a seven-week regimen of radiation therapy in combination with temozolomide, a drug that interferes with DNA replication. The average length of survival after diagnosis for these patients is 14 months, with about eight months after treatment until signs of disease progression emerge.

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My laboratory has been looking for other drugs that might, in combination with radiation therapy, improve the odds for these patients. As a result of the work that we have done in cell and animal models, we are currently running a phase II clinical trial to augment the standard treatment of GBM with the addition of a drug called valproic acid, an inhibitor of the enzyme histone deacetylase (HDAC) (see "Balancing Silence: How a Cell's Fate Is Determined," page 22).

From Cell Lines to Human Trials

HDACs are a class of enzymes that are involved in epigenetic regulation—they modify (deacetylate) the histone proteins that in turn interact with DNA to restrict or encourage gene expression. Altered HDAC activity has been seen in several cancers and appears to prevent the expression of tumor suppressor genes, so there has been a great deal of interest in developing HDAC inhibitors as cancer therapeutics.

Some work in the 1980s also indicated that HDAC inhibitors might enhance the sensitivity of tumor cells to radiation, but the available compounds at the time were not suitable for administration to people.

Another scientist here at the NIH, Philip Tofilon, Ph.D. (who has since moved to the H. Lee Moffitt Cancer Center in Florida), had the idea to revisit this therapeutic possibility with the newer generations of HDAC inhibitors that were being developed. In 2004, my team collaborated with Dr. Tofilon to publish research showing that an HDAC inhibitor, MS-275, enhanced the lethal effects of radiation on tumor cells. Unfortunately, we were not able to develop a collaboration with the company that makes MS-275 to continue this line of work, but we were encouraged enough by our results to jump at the suggestion from our colleague, Howard Fine, M.D., Chief of the Neuro-Oncology Branch at CCR, that another HDAC inhibitor—valproic acid—might be an even better choice for enhancing radiation sensitivity. Valproic acid has long been used in the treatment of epilepsy, which means we know it is safe to use in people and will be transported across the barrier that restricts blood-borne molecules from entering the brain.

So we went back and repeated our experiments with valproic acid instead of MS-275. In general, we go through a staged process of testing potential drugs in the laboratory. First, we perform what is known as a clonogenic survival—essentially, we irradiate tumor cells in a dish with or without the compound to see if it affects cell survival. Then we study the cellular mechanisms that might be responsible for the altered survival—regulation of the cell cycle and various cell death programs. Once we are confident that we have a strong result in cell lines, we move to testing animal models. Often, it is sufficient to introduce the cancer cell line of interest under the skin of a mouse and study the resulting tumor formation, but because there are special problems with drugs reaching the brain, my laboratory uses orthotopic models in which a glioblastoma cell line is implanted directly into the mouse brain.

Mouse models are, of course, only models. For example, GBMs in people are highly invasive, whereas they are not in our animal models. And in order to introduce human cancer cell lines into these mice, we need to genetically impair their immune systems so that they do not reject the grafts. However, strong data that the drug is crossing into the brain and affecting tumors in animal models are usually sufficient to start trials in people.

(*Photo*: R. Baer)

Deborah Citrin, M.D., and Kevin Camphausen, M.D., prepare a patient for image-guided radiation treatment in an advanced tomotherapy unit.

We are still enrolling patients in our clinical trial for the use of valproic acid to enhance radiation sensitivity in the standard of care regimen for GBM. One challenge that we face is purely practical—unlike many other courses of radiation treatment, the treatment for GBM is protracted. We put the patient on the treatment table every day for a seven-week course of radiation. Thus, it can be difficult to recruit patients who do not live in the vicinity of the NIH.

Advanced Technology

One might imagine that a radiation oncologist could simply use the sophisticated technology at his disposal to visualize the tumor, aim a beam of ionizing radiation at it, and pull the trigger. Unfortunately, the situation is not nearly so straightforward. Instead, the machines that we use to visualize the tumor in the patient's body are distinct from the machines that we use to deliver radiation. Thus, when we physically immobilize the patient in the CT scanner, we use lasers on the wall to place marks on the patient's body so that we know their alignment with respect to the scanner. We send the patient home, and then we analyze the images and determine the size and position of the beam that we need to use in the subsequent treatment sessions.

Three days later, when the patient is brought in for the radiation treatment, we use another set of lasers to align the marks we made previously and position the patient on the Linac table. We do everything we can to ensure that the patients are placed in precisely the same position every day of their treatment including, for example, the use of frames to constrain head movements, but even a millimeter's difference can affect the targeting of the beam, and this can be especially challenging over the course of a long treatment due to physical changes, such as weight loss, that invariably occur.

New medical technologies are being developed that will make this process less cumbersome and more accurate. Image-guided radiotherapy (IGRT) is emerging as a very precise method of delivering radiation. My colleague, Deborah Citrin, M.D., has a protocol open that is using a tomotherapy unit—a CT scanner that delivers a thousand times higher voltages than those used for diagnostic purposes—allowing us to take very accurate CT

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images of the patient and deliver intensity-modulated radiation focally to the tumor. For this particular protocol, she is currently treating patients with metastatic disease outside of the brain, but only in a few tissue sites. The entire course of treatment can be delivered in one week, as compared to the standard seven-week course of radiation.

The Side Effects of Radiation

Although we do our best to irradiate the tumor and spare the healthy cells, cancers are never precisely delineated from their surrounding tissue. Usually, normal tissues can repair the damage caused by radiation, but occasionally these tissues are harmed, resulting in serious side effects. Dr. Citrin has several protocols to assess normal tissue toxicity and to use laboratory methods to predict which patients will experience radiation toxicity.

Most of what we know about radiation damage is from lung cancer. The lung is much easier to study than other organs—X-rays reveal damage more easily, lung function can be measured with a simple pulmonary function test, and the cancer patient population is relatively large. However, different tissues are likely to respond differently to radiation damage. Dr. Citrin is currently conducting a protocol for patients with gastrointestinal malignancies, testing blood, urine, and stool for a wide range of markers of damage and inflammation that may predict malabsorption and other dysfunctions of the gastrointestinal tract.

Cognitive decline is of course a devastating risk of therapies for brain cancers. I am working with Patricia Steeg, Ph.D. (see "Going after the Real Killer: Metastatic Cancer," page 12), to study the effects on cognition of radiation therapy for brain metastases from breast cancer. While whole brain radiation therapy can be very effective at destroying these metastases, it is also quite toxic. Through a grant from the Department of Defense specifically aimed at studying brain metastases of breast cancer, we have opened a trial to test prospectively what happens to a patient's neurocognitive status after whole brain irradiation. Women with breast cancer have typically had a chemotherapeutic agent with its own effects on neurocognition, which has been one of the problems with trying to accurately assess the effects of whole brain irradiation.

Measuring Success

GBM is probably many diseases. We know that the tumors do not all result from the same set of genetic mutations. Because it is a relatively rare disorder, we are only just beginning to gather enough patient data to distinguish subtypes. As we are discovering for other cancers, a one-size-fits-all approach to therapy is unlikely to be the answer.

Beyond subtyping the initial tumors, we are very much interested in finding a way to measure the response to therapy as early as possible. How has the tumor responded to four doses of radiation? Are we having any effect? Can we see any differences in the response to treatment for cases in which the cancer recurs? In our animal models, we biopsy the tumors at regular intervals to test the efficacy of our treatments, but this approach is not an option for human patients.

In collaboration with Marsha Moses, Ph.D., at Children's Hospital Boston (part of Harvard Medical School), we are studying biomarkers in the urine that might give us some answers. A few years ago, we published some preliminary evidence in the *Journal of Clinical Oncology* that levels of two protein markers of angiogenesis—vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMPs)—might correlate with recurrence of cancer after radiotherapy. Our hypothesis is that these markers reflect renewed tumor growth and the recruitment of new vascular supplies.

Based on this work, we decided to conduct a large clinical trial to assess these urinary biomarkers in GBM patients through the Radiation Therapy Oncology Group—a multi-institutional, international clinical cooperative group funded by NCI. We gathered urine samples from 204 patients with GBM on the first day of treatment, the last day of treatment, and one month later. We will compare the biomarkers with the incidence of recurrence after one year. The data will be unblinded later this year. If successful, these biomarkers could mean being able to treat those patients with a high likelihood of recurrence much more aggressively before it is too late.

To learn more about Dr. Camphausen's research, *please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=camphausen.*

To learn more about the Radiation Oncology Branch *at CCR, please visit http://ccr.cancer.gov/labs/lab.asp?labid=52.*

One Woman's Story

(Photo courtesy of S. Lassiter)

Sharon Lassiter shows no signs of recurring brain cancer two years after an experimental treatment for glioblastoma multiforme.

Before the headaches started in April 2006, Sharon Lassiter was the picture of health and energy. A mother of two preteens with a full-time position as Deputy Inspector General at Bolling Air Force Base in Washington, D.C., she also found time to be an active member of her church, participate in various clubs, and take spinning classes to keep in shape. "I was go-go-go all the time," she admitted.

Along with the headaches, Lassiter saw flashes in her right eye and developed sensitivity to light, which led the doctors to believe she was having eye migraines. The doctors prescribed migraine medicines, which did not help for very long. "It got to the point that I was wearing sunglasses at work," she said. Then, she started to get dizzy spells and eventually found that she was having more and more difficulty producing the reports that were essential to her job. "I would get home from work and would just go to bed."

As her condition worsened, her eye doctor realized that the problem was neurological and recommended that she have her primary care physician do a computed tomography (CT) scan and use magnetic resonance imaging (MRI). Walter Reed Hospital handled the next phase of her diagnosis and quickly determined that Lassiter had an advanced glioblastoma measuring 3–4 centimeters across in her left occipital cortex. The doctors at Walter Reed sent her to the NIH to determine if she would be eligible to participate in a clinical trial.

"Without treatment, they said I would have 3–4 months to live." The doctors told Lassiter about a trial being conducted by Kevin Camphausen, M.D., to test the efficacy of valproic acid in addition to the standard of care treatment of radiation and temozolomide after surgery to remove the bulk of the tumor. "I had already prayed about it and decided I would participate," said Lassiter, but she went to see Camphausen with her mother who asked several questions about the prognosis and the treatment. "I liked how they handled it. He explained it in detail and was positive about the possibilities."

Once the treatments started, Lassiter refocused her unflagging energies on the treatment process. "I didn't care what I had to do… The procedure was 10–15 minutes on the table. They made this thing to hold your head down and marked it to make sure they were in the right spot. They played music if you wanted." The staff helped her prepare for the changes she would experience, like the "mental fog" she would feel at the start of the treatment. "Sometimes they were down to the day [in predicting the changes]. It helped that I was prepared."

Lassiter also experienced mild hallucinations from the medication. "There was this lady beside me in the elevator, and I thought she had a beard. I told the doctor, and we laughed about it. He said that was something the valproic acid could cause, and I shouldn't worry but that I should tell him if the hallucinations got overpowering."

Lassiter went off the medications in November, 2008, and the MRIs she has every three months are tumor free. She was supposed to complete a full two years on the regimen as part of the protocol but found that the side effects were becoming unmanageable. She is, however, participating in another protocol to discover urinary biomarkers that could signal recurrence of the tumor. "I said 'sure'—anything to help someone else with this disease."

As a result of the trauma her brain has suffered, Lassiter has had some loss of vision and experiences problems with balance. The intense lifestyle she once led has given way to a calmer way of living. "To me, that was the hardest part, learning to just take care of me," she noted. "But, now that I've slowed down, I can enjoy my friends and family that much more.

"I have my faith in God, and I know that he's the reason I was able to come to the right place. He blessed my doctors to have the technology, capability, and smarts to be able to do what they do." However, she added, "I do believe that if I didn't want to fight through this, I'd probably be dead."